jc618 U.S. PTO 11/23/98

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PTO/SB/05 (4/98)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	130-125
First Inventor or Application Identifier	Thomas W. Astle
Title	ULTRA HIGH THROUGHPUT BIOASSAY...
Express Mail Label No.	EM69113008US

jc526 U.S. PTO 09/196046 11/23/98

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231**

1. [X] * Fee Transmittal Form *(e.g., PTO/SB/17)* *(Submit an original and a duplicate for fee processing)*
2. [X] Specification [*Total Pages* 34]
   (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [X] Drawing(s) *(35 U.S.C. 113)* [*Total Sheets* 11]
4. Oath or Declaration [*Total Pages* 45]
   a. [X] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d)) *(for continuation/divisional with Box 16 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

** NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).*

5. [ ] Microfiche Computer Program *(Appendix)*
6. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Copy
   b. [ ] Paper Copy (identical to computer copy)
   c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
9. [ ] English Translation Document *(if applicable)*
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [ ] Preliminary Amendment
12. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
13. [X] * Small Entity Statement(s) *(PTO/SB/09-12)* [ ] Statement filed in prior application, Status still proper and desired
14. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
15. [ ] Other: .....

16. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*
    [ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No: _____/_____
    Prior application information: Examiner _____ *Group / Art Unit:* _____

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

[X] *Customer Number or Bar Code Label* 21091 *(Insert Customer No. or Attach bar code label here)* *or* [ ] *Correspondence address below*

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Address					
City		*State*		*Zip Code*	
Country		*Telephone*		*Fax*	

Name (Print/Type)	John H. Crozier	*Registration No. (Attorney/Agent)*	30,371
Signature	John H. Crozier	*Date*	November 23, 1998

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FEE TRANSMITTAL

Patent fees are subject to annual revision on October 1. These are the fees effective October 1, 1997. Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12. See 37 C.F.R. §§ 1.27 and 1.28.

TOTAL AMOUNT OF PAYMENT ($) 539.00

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Thomas W. Astle
Examiner Name	
Group / Art Unit	
Attorney Docket No.	130-125

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 03-3838
Deposit Account Name: John H. Crozier

[ ] Charge Any Additional Fee Required Under 37 C.F.R §§ 1.16 and 1.17
[ ] Charge the Issue Fee Set in 37 C.F.R § 1.18 at the Mailing of the Notice of Allowance

2. [xx] **Payment Enclosed:**
[xx] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	790	201	395	Utility filing fee	380
106	330	206	165	Design filing fee	
107	540	207	270	Plant filing fee	
108	790	208	395	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 380

2. EXTRA CLAIM FEES

	Extra Claims		Fee from below	=	Fee Paid
Total Claims 29	-20** = 9	X	9	=	81
Independent Claims 5	- 3** = 2	X	38	=	78
Multiple Dependent				=	

***or number previously paid, if greater; For Reissues, see below*

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	82	202	41	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	82	209	41	** Reissue independent claims over original patent
110	22	210	11	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 159

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	950	217	475	Extension for reply within third month	
118	1,510	218	755	Extension for reply within fourth month	
128	2,060	228	1,030	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,320	241	660	Petition to revive - unintentional	
142	1,320	242	660	Utility issue fee (or reissue)	
143	450	243	225	Design issue fee	
144	670	244	335	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))	
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)

SUBMITTED BY

				Complete (if applicable)	
Typed or Printed Name	John H. Crozier			Reg. Number	30,371
Signature	John H. Crozier	Date	11/23/98	Deposit Account User ID	21091

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PATENT
130-125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re US Patent Application of)
Thomas W. Astle)
Filed: Simultaneously herewith.)
Title: ULTRA HIGH THROUGHPUT)
BIOASSAY SCREENING SYSTEM)

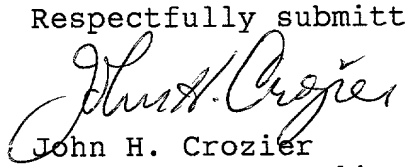
Assistant Commissioner for Patents
Washington DC 20231

"EXPRESS MAIL" MAILING LABEL NO. EM469113008
DATE OF DEPOSIT: NOVEMBER 23, 1998

Dear Sir:

I hereby certify that the enclosed, above-identified patent application, including Specification (34 pages), Drawing (11 sheets), Claims (29), and filing fee, is being deposited by me, postage prepaid, with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date set forth above, addressed to, Assistant Commissioner for Patents, Washington DC 20231.

Respectfully submitted,



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ULTRA HIGH THROUGHPUT BIOASSAY SCREENING SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

Benefit is claimed of the filing dates of United States Provisional Patent Applications Nos. 60/067,895, filed December 8, 1997, and titled ULTRA HIGH THROUGHPUT BIOASSAY SCREENING SYSTEM AND METHOD; 06/073,329, filed February 2, 1998, and titled ULTRA HIGH THROUGHPUT BIOASSAY SYSTEM AND METHOD; and 06/095,497, filed August 6, 1998, and titled USE OF CONTINUOUS CARRIER TAPE FOR POLYMERASE CHAIN REACTIONS, the disclosures of which applications are incorporated by reference hereinto.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to bioassay screening generally and, more particularly, but not by way of limitation, to a novel system for ultra high throughput bioassay screening.

Background Art

High Throughput Screening (HTS) has been in use for at least the past ten years to screen large numbers of potential chemical compounds that may have pharmaceutical efficacy or which may be precursors to pharmaceuticals. A given investigation may involve the screening of on the order of about 10,000 compounds per day. There are three basic areas of HTS: (1) handling the

compound library, (2) lead discovery, and (3) lead optimization. Handling the compound library is an essential element of the other two. Lead discovery and lead optimization tend to overlap. The objective of lead discovery is to develop "hits" or what appear to be active compounds in specific areas. Lead optimization is a refinement of these "hits" so as to pass on qualified leads to medicinal chemistry for further development. Without this refinement, medicinal chemistry is swamped and the discovery of more "hits" is negated. The success of HTS has fostered the next step – a tenfold increase in throughput or Ultra High Throughput Screening (UHTS).

The primary objective of UHTS is to achieve more qualified lead compounds. In general terms, UHTS has been described as the ability to screen, in a given investigation, a library of 500,000 compounds against 50 therapeutic targets per year. This equates to 100,000 compounds screened per day. The economics of this number dictates some form of miniaturization to conserve the precious reagents consumed.

Since compound handling is the front end of both lead discovery and optimization, it must be considered first. The long term library storage is necessarily in solid or semi-solid form, for stability reasons. However, for use in screening, the library must be converted to a liquid phase. The most commonly accepted method of such conversion is to weigh out a small aliquot of a compound and solvate it with dimethyl sulfoxide (DMSO). Speed and convenience dictate weighing out typically 10 milligram quantities as the minimum amount. These are then brought into solution form, at, say, 10

millimolar concentration, yielding 5 to 10 ml of solution. This is then subdivided into smaller aliquots of 0.5 ml and stored frozen in sets of 96 deepwell tubes at – 20 or –80 degrees Centigrade as an archive library.

Several areas of concern arise in going from the archive library to the usable form for the assay. First is the concentration – many assays are tested at 10^{-5} or 10^{-6} concentrations. The majority of assays cannot tolerate much more than 1% DMSO. Thus, a dilution from the archive library is required. However, some compounds, while soluble in 100% DMSO, are not soluble in lesser percentages. It is desirable to make the compound dilution in the final assay volume and not in a previous dilution step. Another concern is protecting the stability or validity of the archive compound. Freezing it lengthens its shelf life. But to access the compound, it must be thawed to remove an aliquot. Each time a freeze-thaw cycle occurs, there is the potential for moisture to degrade the compound. Thus, it is desirable to minimize these cycles. The real problem is how to transfer 100,000 discreet samples per day from the archive library to the assay, keeping the above constraints in mind.

Since the libraries may contain upwards of 500,000 discreet compounds, a means is required to both aspirate multiple samples from the compound source and dispense multiple aliquots of nanoliter quantities into the assay destination. Since in the majority of biological assays, a concentration of more than 1% DMSO is toxic to the assay results and if an assay is to run at a 5 microliter volume, only 50 nanoliters of DMSO is allowed. The molarity of the compound solution in DMSO is adjusted so that 50 nanoliters of the compound solution also

provides the desired concentration of compound to the assay.

Small individual piezo electric pumps have been utilized for the purpose of aspirating and dispensing these small quantities of liquids. The common method is for the piezo to squeeze an individual glass capillary to create a pressure wave to dispense liquid from within the capillary. Reversing the action will cause the capillary to aspirate liquid. The individual piezo pumps are costly to manufacturer, as are the electronics to drive them. In the pharmaceutical application, described above, it is necessary to rinse the flow passage with a suitable solvent, normally DMSO, to prevent sample-to-sample carry over. Due to the small displacement volume of the piezo pump device a considerable number of cycles or shots is required to pass a suitable quantity of wash fluid. The wash fluid must then be cleared from the pump so as not to dilute the next sample.

In such pharmaceutical research, due to the high numbers to be processed, the samples to be aspirated and dispensed are on very close centers, typically 4.5mm, or 2.25mm, or smaller. This places a severe limit on the size of the dispensing device. Due to the small quantities involved, more efficient liquid movement is obtained if the device causing fluid motion is close to the outlet orifice. Otherwise, the energy of the shockwave causing displacement is absorbed by the liquid in the pathway. This results in less velocity at the orifice. If the stream does not have sufficient velocity and kinetic energy at the orifice, it does not overcome the surface tension there and the form of delivery is as liquid drops; however, an ejected stream is desired especially when dispensing. This

permits non-contact dispensing. The dispensing tip is not contaminated with other fluids - only the fluid being dispensed.

Accordingly, it is a principal object of the present invention to provide method and means for ultra high throughput screening.

It is a further object of the invention to provide such method and means that are economically implemented.

It is an additional object of the invention to provide such method and means that permit the economical simultaneous aspirating and dispenses of a large number of very small volumes of liquid.

It is another object of the invention to provide such method and means that provide for the compact storage of large numbers of chemical compounds.

It is yet a further object of the invention to provide liquid transfer method and means that employs a single piezoelectric crystal to simultaneously effect the aspiration or dispensing of a large number of liquid samples.

Other objects of the present invention, as well as particular features, elements, and advantages thereof, will be elucidated in, or be apparent from, the following description and the accompanying drawing figures.

SUMMARY OF THE INVENTION

The present invention achieves the above objects, among others, by providing, in a preferred embodiment, a method of performing biological assays, comprising: providing a longitudinally extending carrier tape having thermally formed therein a plurality of reagent receiving wells; adding a reagent to each of said reagent receiving wells; permitting each of said reagent receiving wells to incubate at a predetermined temperature for a predetermined time; and performing a biological analysis on each of said reagent receiving wells.

BRIEF DESCRIPTION OF THE DRAWING

Understanding of the present invention and the various aspects thereof will be facilitated by reference to the accompanying drawing figures, provided for purposes of illustration only and not intended to define the scope of the invention, on which:

Figure 1 is a top plan view of a carrier tape, having a plurality of bioassay wells formed therein, and constructed according to one aspect of the present invention.

Figure 2 is a fragmentary, side elevational view, in cross-section, of the carrier tape of Figure 1.

Figure 3 is a fragmentary, isometric view, of a sealing layer for use over the carrier tape of Figure 1.

Figure 4 is a fragmentary, side elevational view, in cross-section, of the mechanism by which the sealing layer of Figure 3 placed on the carrier tape of Figure 1.

Figure 5 is a fragmentary, side elevational view, in cross-section, of the mechanism by which the sealing layer of Figure 3 is removed from the carrier tape of Figure 1.

Figure 6 is an isometric view of a portion of a carrier tape inserted in a frame.

Figure 7 is side elevational view, in cross-section, of the carrier tape and frame of Figure 6.

Figure 8 is a schematic view of a polymerase chain reaction (PCR) processing line employing the present invention.

Figure 9 is a schematic detail of a portion of Figure 8.

Figure 10 is a schematic, isometric view of a PCR processing line including an incubator.

Figure 11 is a fragmentary, isometric view of a tractor drive for moving the carrier tape of Figure 1.

Figure 12 is a schematic, isometric view of a compound transfer station employing the present invention.

Figure 13 is a greatly enlarged, side elevational view, in cross-section, of a dispensing/aspirating needle constructed according to the present invention.

Figure 14 is a side elevational view, partially in cross-section and partially schematic, of a dispensing/aspirating system according to the present invention.

Figure 15 is an enlarged, fragmentary, isometric view of a dispensing/aspirating system according to the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reference should now be made to the drawing figures on which similar or identical elements are given consistent identifying numerals throughout the various figures thereof, and on which parenthetical references to figure numbers direct the reader to the view(s) on which the element(s) being described is (are) best seen, although the element(s) may be seen on other figures also.

In one aspect of the invention, there is adapted a sprocket driven carrier tape, as a processing vehicle for biological assays. A similar type of tape is known in the electronics industry for transporting electrical components, such as is described in Electronic Industries Association documents EIA/IS_704 and others.

Figure 1 illustrates a carrier tape, constructed according to the present invention, and generally indicated by the reference numeral 20. Carrier tape 20 is made from a heavy film, 15 to 20 mils thick, of a thermoformable resin. The type of resin used depends on the application. Polypropylene is a suitable candidate for those applications requiring chemical resistance. Polycarbonate film is a candidate for those applications involving growth, or supporting growth, of tissue culture and it may be supplied clear for colorimetric type assays. Polycarbonate or other materials may be supplied opaque, white, or black for fluorometric or luminescent assays.

Carrier tape 20 includes a substrate 28 which is processed to emboss therein a plurality of wells, as at 30, in specific patterns to hold liquid. A plurality of sprocket drive holes, as at 32, is provided along each edge. Sprocket drive

holes 32 are precision punched to maintain a uniform spacing. This permits tractor driving carrier tape 20 for transport. Sprocket drive holes 32 also create a positional relationship to define any location on carrier tape 20 to provide recall to any selected well on the carrier tape.

The shape of wells 30 is a function of the application for carrier tape 20. For chemical compound storage, the walls of the wells may have a Vee shape with a rounded bottom, as shown on Figure 2. For assays requiring an optical readout, the well may have a clear flat bottom. The required well shape is derived from the embossing tool.

The pattern of wells 30 is also a function of the application of carrier tape 20. The defacto standard for biological assays is the 96-well microplate (see Society for Biomolecular Screening 96-well plate standard). This is an 8 x 12 matrix of wells or receptacles on 9-mm center spacing. The need for higher numbers of assays and their miniaturization is fostering higher density formats. To be compatible with existing instrumentation and chemical libraries, these new formats are multiples of the 96-well format. The 384 -well format is a 16 x 24 matrix on 4.5mm centers. The 1536-well format is a 32 x 48 matrix on 2.25mm centers. Any of these formats may be embossed in carrier tape 20 (Figure 1). Carrier tape 20 has been embossed with a group 40 of wells 30. It will be understood that a plurality of additional such groupings will be provided axially along the length of the carrier tape.

Carrier tape 20, with its sprocket or tractor drive, provides a fast efficient way of transporting the reagent receiving patterns through the processing

equipment. The inline processing provides considerable throughput advantages over handling the reagent patterns in individual injection molded plates. To provide pattern identification, each pattern on a roll of carrier tape is supplied with both a man readable identification number 50 and a machine readable identification number, in this case, a bar code 52, both printed on the bottom side of carrier tape 20 using ink jet or other suitable methods.

Another primary advantage of the use of carrier tape 20 is compact storage. One hundred thousand chemical compounds for UHTS, in 5 microliter aliquots, can be stored in a carrier tape roll 4 inches wide and 16 inches in diameter. This storage requires that the liquid contents of the wells be sealed with a leak tight seal. A further requirement, since later access to the liquid wells is required, is that the seal must be removable.

For chemical compound storage the carrier tape and seal material must be inert to both the chemical compound and the dimethyl sulfoxide (DMSO) used to solvate the compound. Polypropylene meets this requirement for the carrier tape. The seal layer may be a pressure sensitive adhesive or a heat seal. If pressure sensitive material is used it must be DMSO resistant. While the latter type of material is available, there is still the question of compatibility with the chemical compounds. For this reason a heat seal material is preferred.

Figure 3 illustrates a heat seal layer, generally indicated by the reference numeral 60. Heat seal layer 60 is a two-part structure made by lamination or co-extrusion. A seal layer 62 is provided which has a low melting point, low tensile strength resin such as a modified low density polyethylene or an ethylene vinyl

acetate copolymer. A top, or support, layer 64 is provided adjacent seal layer 62 and is a high temperature resin with good tensile strength properties. Polyester is commonly used. The high melting point of the polyester prevents it from sticking to the heat seal apparatus at the temperature required to bond the seal layer. The high tensile strength of the polyester supports the seal layer during seal and unseal operations. This type of bi-film is commonly used in lidding applications for the prepared food industry.

To obtain a valid leak proof heat seal requires that the carrier surface and the heat seal surface be held in intimate contact for the sealing period. The sealing period is a function of time and pressure. The carrier tape is indexed with an intermittent motion, such as that which is obtained with a walking beam drive.

As is illustrated on Figure 4, at a sealing station, carrier tape 20 is held flat by means of a vacuum platen 80. Sealing layer 60 is fed from a roll (not shown) to a position between a heated sealing head 82 and carrier tape 20. Heated sealing head 82 brings sealing layer 60 and carrier tape 20 together under defined conditions of time, pressure, and temperature.

Air entrapped between the seal layer 62 and carrier tape 20 (Figure 1) will inhibit the seal. To avoid this, carrier tape 20 is provided with a plurality of vent holes, as at 70, spaced between wells 30. This allows a vacuum platen 80 supporting carrier tape 20 to evacuate any entrapped air between the two films, effecting a leak proof seal.

Removal of seal layer 60 may be achieved two ways. Figure 5 illustrates an automated system in which sealed carrier tape 20 is passed under a heated

roller 90. Polyester top layer 64 prevents sticking to roller. Roller temperature and contact time are controlled by the machine parameters. Seal layer 62 is softened and the strength of polyester layer 64 is used to separate the seal. A take up winder (not shown) on which seal layer 62 is wound, provides the tensile force necessary to break the seal. Carrier tape 20 is held down by edge guides 92 that are outside of the sealed pattern.

Some biological materials may be degraded by the heat from the unsealing. To eliminate that possibility, vacuum platen 80 supporting carrier tape 20 at the unsealing station may be refrigerated.

There are two basic applications of carrier tape 20 - use with automated systems and use with manual systems. This is particularly true where carrier tape 20 is used for chemical compound storage for pharmaceutical screening. Use of carrier tape 20 for that concept provides an exceptional method for the central compound library to distribute aliquots of compounds to outlying investigators. Each pattern 40 of compounds on the carrier tape has its own identification number imprinted on it. It may be cut from the carrier tape and handled as a separate entity. This creates the need of different solutions to handle individual patterns.

As is illustrated on figures 6 and 7, with manual systems, the primary usage of the present invention is the introduction of compounds into assays performed in microplates. This is accomplished with a special frame of two-part construction, the frame having an outer shell 100 (Figure 6) with an internal opening which meets the external footprint of the standard for a 96-well

microplate. Thus, it will fit instrumentation designed for such microplates. An inner retainer 102 (Figure 7) snaps into the outer frame to support a section of carrier tape pattern 104. Inner retainer 102 holds flat carrier tape 104 to facilitate aspirating liquid from the wells with a multiple tip pipettor consisting of 384 or 96 tips.

Special requirements are required to unseal the individual section of carrier tape pattern 104. It is desirable to unseal the pattern 104 after it is retained and used in outer shell frame 100. The edge of the seal on carrier tape 104 is clamped between outer shell frame 100 and inner retainer 102. For manual use, the seal is die cut with a steel rule die (not shown). It is die cut within the confines of the outer frame. Thus, a user can catch an edge of and strip carrier tape section 104 from the well area.

Most chemical compounds are solvated in dimethyl sulfoxide (DMSO). DMSO freezes at –4°C (-4°F). To minimize compounds being removed with the seal, inner retainer 102 is chilled prior to assembly of carrier tape section 104 in the frame. This is sufficient to solidify the DMSO to assure that the compounds remain in the wells and are not removed with the seal.

In normal operation, rolls of carrier tape 20 (Figure 1) filled with chemical compound aliquots would be stored frozen at –20°C or even –80°C. The compact nature of this storage system allows a very large number of chemical compounds to be stored in one freezer. Once removed from the freezer, the carrier tape system has a minimum of latent heat storage, both in the tape itself and in the small volume of liquid it contains. This has the advantage of a quick defrost prior

to use, whereas microplate storage systems may require the better part of a day to defrost.

The disadvantage of the quick defrost is that the time in handling the roll may exceed the defrost time. The handling of the sealed roll may cause some of the well contents to move away from the bottom of the well. This is compensated for, by spinning the roll on its unwind stand prior to use in the application. Centrifugal force will move the liquid to the well bottom. Surface tension will retain it there during the gentle handling of the unwind stand during processing.

Biological assays and protocols utilizing polymerase chain reaction (PCR) require multiple cycles of different temperatures, usually three. These protocols are currently processed in microplates, 96-well or 384-well. A microplate is placed in its own thermal cycling instrument. Because of the latent heat capacity of the microplate, the majority of processing time is due to changing the temperature of the microplate - not the reagent it contains. The carrier tape system of the present invention will greatly improve the speed of processing PCR, a vital protocol in the Human Genome Project and other genomic studies.

The small latent heat capacity of the carrier tape and its speed of precise movement open a new vista for PCR. Instead of cycling temperature about a fixed microplate, the carrier tape can be quickly transported from one temperature station to the next as illustrated on Figure 8 which shows a PCR processing line employing the present invention. A first reagent processor, generally indicated by the reference numeral 120, is provided and a second reagent processor, generally indicated by the reference numeral 122 may also be provided. Similar additional

reagent processors can be provided as needed. Suitable motive means indexes carrier tape 20 to the right on Figure 8. A first pipettor 130, which may be assumed to be a 384-well pipettor, adds a first set of reagents to wells 30 (Figure 1) on carrier tape 20. Sealing film 60 is fed from a supply roll 140 to a sealing station comprising a heat seal bar 142 which provides closure by applying pressure and heat to seal layer 60 and carrier tape 20 and a heat seal anvil 144 backs up the seal bar. Heat seal anvil also applies vacuum to hold carrier tape 20 flat similar to vacuum platen 80 (Figure 4). The application of vacuum will also evacuate any entrapped air between seal layer 60 and the surface of carrier tape 20.

Carrier tape 20 then indexes through a series of temperature control stations, as at 150. The time at each station 150 is a function of the index time. In many applications, a common temperature dwell time is satisfactory. In those protocols where a common time is not acceptable, an individual temperature station would be opened at its selected time interval.

As illustrated more clearly on Figure 9, in addition to having a heated bottom portion 160, each temperature control station has a heated lid 162. This provides quick uniform temperature to the contents of the wells.

Continuing to refer to Figure 9, after passing through the required temperature cycles, seal layer 60 may be removed for access to the contents of the wells. As described before, a heated roll 70 warms the seal area. A seal winder 172 provides tension on the seal layer 60, to remove it from carrier tape 20. With the wells open, the contents may be removed or additional reagents added. In the

latter case, a second pipettor 180 adds the second set of reagents and the entire protocol repeated on second reagent processor 122.

Each temperature station 150 is maintained at a fixed, easily regulated temperature. As carrier tape 20 is indexed to each station 150, the temperature of the small volume of reagents within the wells will quickly reach the equilibrium temperature of the specific station.

Due to the small volume of reagents in the wells and the high temperature of PCR (typically 90°C), evaporation is a real concern. Another concern is contamination, well to well, due to the high amplification of PCR. The ability to seal each well with a leakproof seal, as described before, provides an ideal solution for both problems. Access to the wells is required at the end of the PCR. The ability to unseal the carrier tape automatically meets that requirement.

Many biological assays require an incubation period following the addition of reagents. The incubation period may have environmental demands (i.e., elevated temperature typically 37°C, high humidity to minimize evaporation from open wells, or a CO_2 environment for cell viability). This may be easily provided on a carrier tape system by cutting the carrier tape into convenient length (i.e. 4 feet long).

A system providing for incubation prior to fluorescence reading is illustrated on Figure 10 where the system is indicated generally by the reference numeral 180. System 180 includes a first supply roll 182 of sealed carrier tape 184, similar to carrier tape 20 (Figure 1), containing a large number of chemical compounds, and a second supply roll 190 of unsealed assay carrier tape 192, also

similar to carrier tape 20, however, having empty wells. As compound tape 194 is unrolled, it passes under a heated roller 196 which removes sealing layer 60 which is wound on roller 198 in the manner described above with reference to Figure 8.

Tapes 184 and 192 are indexed under a compound transfer manifold 210 which transfers chemical compounds from the wells on compound carrier tape 184 to the wells on assay carrier tape 192. Compound carrier tape 184 can then be discarded as by means of a tape cutter 220 and a waste container 222.

After the transfer of chemical compounds by compound transfer manifold 210, assay carrier tape 192 is indexed under a first reagent manifold 230 for introduction of reagents into the wells on the tape, then, if required, under a second reagent manifold 232 for the introduction of additional reagents, and then, if required, one or more additional reagent manifolds. Assay carrier tape 192 is then indexed under a standards and controls manifold 234 and then under a tape cutter 236 where the tape is cut into, for example, 4-foot lengths. The cut lengths of assay carrier tape 192 are then transported, using a tractor drive, into an incubator 240. Incubator 240 can be very compact, with a unit 6 inches wide by 24 inches deep by 4 feet long accommodating 100,000 wells of the type described above with reference to Figures 1 and 2. After the required incubation period, each strip moves to the next processing station, in this case a fluorescence reader 244 which may read, for example, fluorescence intensity, fluorescence polarization, luminescence, or time resolved fluorescence. After reading, each

section of tape 192 can then be disposed of by means of a tape cutter 250 and a waste container 252.

Figure 11 illustrates the major components of a tractor drive for moving carrier tape 20. A motor 270, which may be a stepper motor, has a rotatable shaft 272 to which is affixed a sprocket wheel 274. Sprocket wheel has a plurality of sprockets, as at 276, extending outwardly from the outer periphery thereof, the sprockets engaging sprocket holes 32 in carrier tape 20. As motor 270 rotates sprocket wheel 274, carrier tape 20 is driven in one direction or the other. One or more sprocket idler wheels 280 are provided to support and guide carrier tape 20. The extent of travel of carrier tape 20 may be determined by an encoder (not shown) associated with one of the rotary components of the tractor drive, by counting the number of sprocket holes 32 passing a given point by optical or other means, and/or by identifying indicia, such as bar code 52 (Figure 1), on the carrier tape.

Figure 12 illustrates a compound transfer system employing the present invention, the system being generally indicated by the reference numeral 300. Here, sealed carrier tape 20 containing a large number of chemical compounds is unrolled from a supply roll 310, sealing layer 60 is removed from the carrier tape by means of a heated roller 312 and a winder roller 314, and the carrier tape is indexed under a 384-well pipettor 316 with a transverse moving head having 384 needles depending therefrom. Such a pipettor may be a Quadra384 Pipettor as furnished by Tomtec, Inc., of Hamden, Connecticut. Included in system 300 are two pairs of dual reversible stackers 320 which, depending on programming,

supply standard 384-well microplates to an six-position X-Y shuttle 330 or accept the microplates from the shuttle. The open wells on carrier tape 20 can be accessed by pipettor 316. Using "pipeline" pipetting, pipettor 316 aspirates the various reagents in the assay using an air gap for separating the reagents. The standards and controls are aspirated from special reservoirs (not shown) to match the user's format. The ability of pipettor 316 to aspirate 0.5 microliter quantities permits aspirating compounds from carrier tape 20 in 100% DMSO, while maintaining a 1% DMSO concentration in the 50 microliter assay volume. In addition, to speed processing, pipeline pipetting uses high volume reagents (i.e., buffer) to wash out the small volume of compound from the pipettor tips, thereby maintaining precision in the assay. After dispensing the tip volume in an assay microplate, the plate is restacked in one of stackers 320, the pipettor tips are washed in an ultrasonic tip wash station (not shown), and the next microplate is infed from a stacker and the cycle is repeated.

After use, carrier tape 20 can be discarded or, if the chemical compounds thereon are to be saved for future use, a sealing layer 60 may be applied and the carrier tape wound on storage roll 340.

Another aspect of the present invention is to provide means to both aspirate and dispense multiple aliquots of nanoliter quantities. The unique principle of this invention is to have one piezo crystal exert sufficient force on multiple tubes to deform them to displace the desired volume. The amount of force, and thus displacement, is controlled by the electronics driving the piezo crystal. The dispensing tubes being deformed remain within their elastic limit.

When the piezo crystal retracts, the cross section of each dispensing tube returns to its original cross sectional area, thereby creating the aspirate/dispense action.

The nanoliter volumes require a very small diameter orifice. This generates the back pressure against the shockwave that creates the stream velocity through the orifice. Not only must the inside diameter be small, but also the wall thickness must be thin, requiring a small outside diameter. A heavy wall section creates additional surface area at the orifice, increasing the surface tension forces. The thin walled small orifice tube results in a fragile dispensing tube. This presents both reliability and manufacturing problems.

The present invention uses a small dispensing needle 400, as illustrated on Figure 13. Typically, the inside diameter of needle 400 is 0.003 inch with an outside diameter of 0.012 inches. This provides a 0.0045-inch wall section. Dispensing needle 400 is fitted inside of a supporting needle 410 having an inside diameter of 0.016 inch allowing a slip fit of the outside diameter of the dispensing needle. Needles 400 and 410 are bonded at the tops thereof with a suitable material, such as UV cured epoxy or polyurethane adhesive, to form a liquid-tight seal 420. Needles 400 and 410 together form a needle assembly, generally indicated by the reference numeral 420.

As shown on Figure 14, each needle assembly 420 is connected with a sleeve 430 of suitable material to a pump tube 432. Pump tube 432 is of a suitable cross section and length for the designed delivery volume. Pump tube 432 is retained between a rigid back up plate, or anvil, 434 and a piezo crystal assembly 436. The available movement of piezo crystal assembly 436 is also a

variable in this equation. As is shown on Figure 15, multiple pump tubes 436 and their associated delivery needle assemblies 420 may be operated by one piezo crystal assembly 436. Piezo crystal assembly 436 is contained within the same anvil assembly 434 such that an increase in size of the piezo crystal causes a decrease in size of pump tubes 432. This provides the necessary pumping action, by displacement. Referring principally to Figure 14, the other end of pump tube 432 is connected to a small fast acting solenoid valve 440 such as used in ink jet printing. During the dispense part of the cycle solenoid valve 440 is closed, blocking flow from pump tube 432 at that end. Only the orifice end of needle 400 remains open to the atmosphere.

Referring again to Figure 15, an individual solenoid valve 440 is connected to each pump tube 432, although only one piezo crystal assembly 436 may be used to squeeze multiple pump tubes. Each solenoid valve 440 is connected through a manifold 450 to a common 3-way valve 452 (Figure 14). Three-way valve 452 selectively connects all solenoid valves 440 to a source of air pressure 460, a source of vacuum 462, or a source of rinse liquid 464. Rinse liquid reservoir 464 is a closed container that is pressurized by a regulated air pressure through a valve 466.

The sequence of operation is as follows. Piezo crystal assembly 436 is energized to an initial holding or home position. This position compensates for any variation in the outside diameter of the multiple pump tubes 432. From this home position, all pump tubes 432 will be compressed the same dimension. The multiple delivery needles 400 are then dipped into the various wells, or reservoirs

470 (Figure 14) containing the liquid to be aspirated. Three-way valve 452 connects all solenoid valves 440 to vacuum source 462. With the tips of delivery needles 400 submerged, solenoid valves 440 open and reclose quickly and are open long enough to allow the vacuum to aspirate liquids up through the area of piezo crystal assembly 436 and into pump tubes 432. Solenoid valve 440 closes before the liquid can reach the interior components of the solenoid valve. The length of pump tube 432 is sized to allow for variations in flow of the different liquids. The minimum flow for each liquid flow path is that the liquid line must pass the end of the pump tubes 432 and not reach the inlet of solenoid valve 440.

With pump tubes 432 filled, delivery needles 400 are moved to the dispense position. Piezo crystal assembly 436 is energized to its set value, causing a uniform and quick constriction of all pump tubes 432. This constriction displaces the fluid within pump tubes 432, causing delivery at the orifice of needles 400.

The next position of delivery needles 400 depends on the system function that is desired. The remaining contents of pump tube/needle assembly 432/400 may be reclaimed back into the origin or they may be deposited in a waste container. This is a similar function, but with the waste disposal, it is combined with the rinse function. The reclaim function is described, as follows. Three-way valve 452 switches to apply air pressure to all solenoid valves 440. With delivery needles 400 in the reclaim position, solenoid valves 440 open. Air pressure blows the remaining contents of the pump tube/delivery needle assembly 432/400 back into the origin reservoir.

Solenoid valves 440 close and needle assemblies are then moved to the waste/rinse position. Three-way valve 452 switches to the rinse liquid supply 464. Solenoid valves 440 open, admitting wash liquid to delivery needles 400, rinsing them to waste. At the completion of the wash cycles, solenoid valves 440 close. Three-way valve 452 then switches to pressure. Solenoid valves 440 open, blowing the remaining wash fluid contents in the system to waste. With the flow passages clear, the entire cycle repeats for the next aspirate/dispense cycle.

The amount of compression on pump tubes 432 is directly related to the volume dispensed from the outlet orifices of needles 400. In turn, the compression imparted by the piezo crystal assembly 436 is a function of its electrical excitation. This relationship is used to control the volume of liquid aspirated or dispensed on each cycle.

A closed loop monitoring system may be provided by locating a fiber optic transmitting and receiving pair 480/482 (Figure 14), looking across each dispensing orifice of a needle 400. Fiber optic pair is 480/482 is connected to a light emitting diode and a phototransistor (not shown). A base line of conduction in the phototransistor is obtained when there is no flow from the orifice. When there is flow from the orifice, the conduction of the phototransistor is varied during the period of flow. This signal may be amplified and used to monitor or control the excitation to piezo crystal assembly 436. Only one piezo crystal assembly 436 is used to operate multiple orifices. Thus, the phototransistor signals would be averaged to provide feedback control to the piezo excitation. The individual orifice signals would be used to monitor flow or no flow from each

orifice on each dispense cycle. If an orifice becomes clogged or otherwise ceases to function properly an error signal may be generated and corrective action can be taken. If individual piezo crystals are used on each pump tube then the photo transistor pair can have full feedback control on each delivery orifice.

In the embodiments of the present invention described above, it will be recognized that individual elements and/or features thereof are not necessarily limited to a particular embodiment but, where applicable, are interchangeable and can be used in any selected embodiment even though such may not be specifically shown.

Terms such as "upper", "lower", "inner", "outer", "inwardly", "outwardly", and the like, when used herein, refer to the positions of the respective elements shown on the accompanying drawing figures and the present invention is not necessarily limited to such positions.

It will thus be seen that the objects set forth above, among those elucidated in, or made apparent from, the preceding description, are efficiently attained and, since certain changes may be made in the above construction without departing from the scope of the invention, it is intended that all matter contained in the above description or shown on the accompanying drawing figures shall be interpreted as illustrative only and not in a limiting sense.

It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described and all statements of the scope of the invention which, as a matter of language, might be said to fall therebetween.

I claim:

1. A method of chemical compound storage, comprising:

(a) providing a longitudinally extending carrier tape having thermally formed therein a plurality of chemical receiving wells; and

(b) adding to each of said chemical receiving wells a chemical compound.

2. A method of chemical compound storage, as defined in Claim 1, further comprising: placing a liquid tight sealing material over said chemical receiving wells to retain said chemical compounds therein and to minimize evaporation.

3. A method of chemical compound storage, as defined in Claim 2, further comprising: forming said carrier tape into a compact roll for storage.

4. A method of chemical compound storage, as defined in Claim 1, further comprising: providing said carrier tape of a thermoformable material having a thickness on the order of from about 15 mils to about 20 mils.

5. A method of chemical compound storage, as defined in Claim 1, further comprising: providing said carrier tape formed of polypropylene to provide solvent resistance.

6. A method of chemical compound storage, as defined in Claim 1, further comprising: providing said carrier tape formed of clear polycarbonate or polystyrene to facilitate optical reading of contents within said chemical receiving wells.

7. A method of chemical compound storage, as defined in Claim 1, further comprising: providing said chemical receiving wells in repetitive matrixes selected from the group consisting of 8x12 wells with a spacing of 9mm between centers, 16x24 wells with a spacing of 4.5mm between centers, and 32x48 wells with a spacing of 2.25mm between centers.

8. A method of chemical compound storage, as defined in Claim 7, further comprising: providing each of said repetitive matrixes with a unique identifier.

9. A method of chemical compound storage, as defined in Claim 2, further comprising: providing said sealing material with a pressure sensitive adhesive to adhere said sealing material to said carrier tape such as to permit removal of said sealing material after adhesion to said carrier tape.

10. A method of chemical compound storage, as defined in Claim 2, further comprising: providing said sealing material heat sealed to said carrier tape such as to permit removal of said sealing material after being sealed to said

carrier tape.

11. A method of chemical compound storage, as defined in Claim 10, further comprising providing said seal material as a two layer material having:

(a) a lower, seal layer of a low melting point material inert to the contents of said chemical receiving wells; and

(b) an upper high melting point layer having a higher tensile strength than said seal layer and being joined to said seal layer, to assist in removing said sealing material from said carrier tape.

12. A method of chemical compound storage, as defined in Claim 11, further comprising: providing said seal layer formed of a material selected from the group consisting of modified low density polyethylene and ethyl vinyl acetate.

13. A method of chemical compound storage, as defined in Claim 11, further comprising: providing said upper layer formed from polyester.

14. A method of chemical compound storage, as defined in Claim 2, further comprising: removing said sealing material from said carrier tape by using a heated roll to warm said sealing material for removal.

15. A method of chemical compound storage, as defined in Claim 2, further comprising: perforating said carrier tape with small holes between said chemical receiving wells to evacuate space between said seal material and

said carrier tape at time of sealing to assure an intimate leak tight seal is achieved between said seal material and said carrier tape.

16. A method of chemical compound storage, as defined in Claim 2, further comprising: die cutting said sealing material around a pattern of said chemical receiving wells to allow manual removal of said sealing material from said carrier tape.

17. A method of chemical compound storage, as defined in Claim 3, further comprising: spinning said roll to force contents of said chemical receiving wells to bottoms of said chemical receiving wells by centrifugal force.

18. A method of chemical compound storage, as defined in Claim 1, further comprising: severing individual patterns of said chemical receiving wells from said carrier tape so that said individual patterns can be used independently.

19. A method of performing biological assays, comprising:

(a) providing a longitudinally extending carrier tape having thermally formed therein a plurality of reagent receiving wells;

(b) adding a reagent to each of said reagent receiving wells;

(c) permitting each of said reagent receiving wells to incubate at a predetermined temperature for a predetermined time; and

(d) performing a biological analysis on each of said reagent receiving wells.

20. A method of performing biological assays, as defined in Claim 19, further comprising: placing a liquid tight sealing material over said reagent receiving wells to retain said chemical compounds therein and to minimize evaporation.

21. A device for chemical compound storage, comprising: a longitudinally extending carrier tape having thermally formed therein a plurality of chemical receiving wells.

22. A device for chemical compound storage, as defined in Claim 21, further comprising: a liquid tight sealing material disposed over said chemical receiving wells to retain said chemical compounds therein and to minimize evaporation.

23. A device for chemical compound storage, as defined in Claim 22, wherein: said carrier tape is formable into a compact roll for storage.

24. A device for performing biological assays, comprising: a carrier tape having thermally formed therein a plurality of reagent receiving wells.

25. A device for performing biological assays, as defined in Claim 24, further

comprising: a liquid tight sealing material disposed over said reagent receiving wells to retain said chemical compounds therein and to minimize evaporation.

26. A liquid aspirating/dispensing device, comprising:

(a) a plurality of cylindrical passageways; and

(b) a single piezoelectric crystal to simultaneously compress said cylindrical passageways to aspirate or dispense liquid by positive displacement within said passageways.

27. A liquid aspirating/dispensing device, as defined in Claim 26, further comprising:

(a) a single fast acting solenoid valve connected to first ends of said cylindrical passageways; and

(b) a plurality of small diameter orifices connected to a second ends of said cylindrical passageways.

28. A liquid aspirating/dispensing device, as defined in Claim 27, wherein: said fast-acting solenoid valve is connected to a three-way valve to selectively connect one of compressed gas, a vacuum source, and a pressurized liquid container to said solenoid valve.

29. A liquid aspirating/dispensing device, as defined in Claim 27, wherein: said

small diameter orifice comprises a thin walled tube with a small inner diameter, said thin walled tube being encased in a larger tube for mechanical support.

30. ABSTRACT

In a preferred embodiment, a method of performing biological assays, including: providing a longitudinally extending carrier tape having thermally formed therein a plurality of reagent receiving wells; adding a reagent to each of said reagent receiving wells; permitting each of said reagent receiving wells to incubate at a predetermined temperature for a predetermined time; and performing a biological analysis on each of said reagent receiving wells.

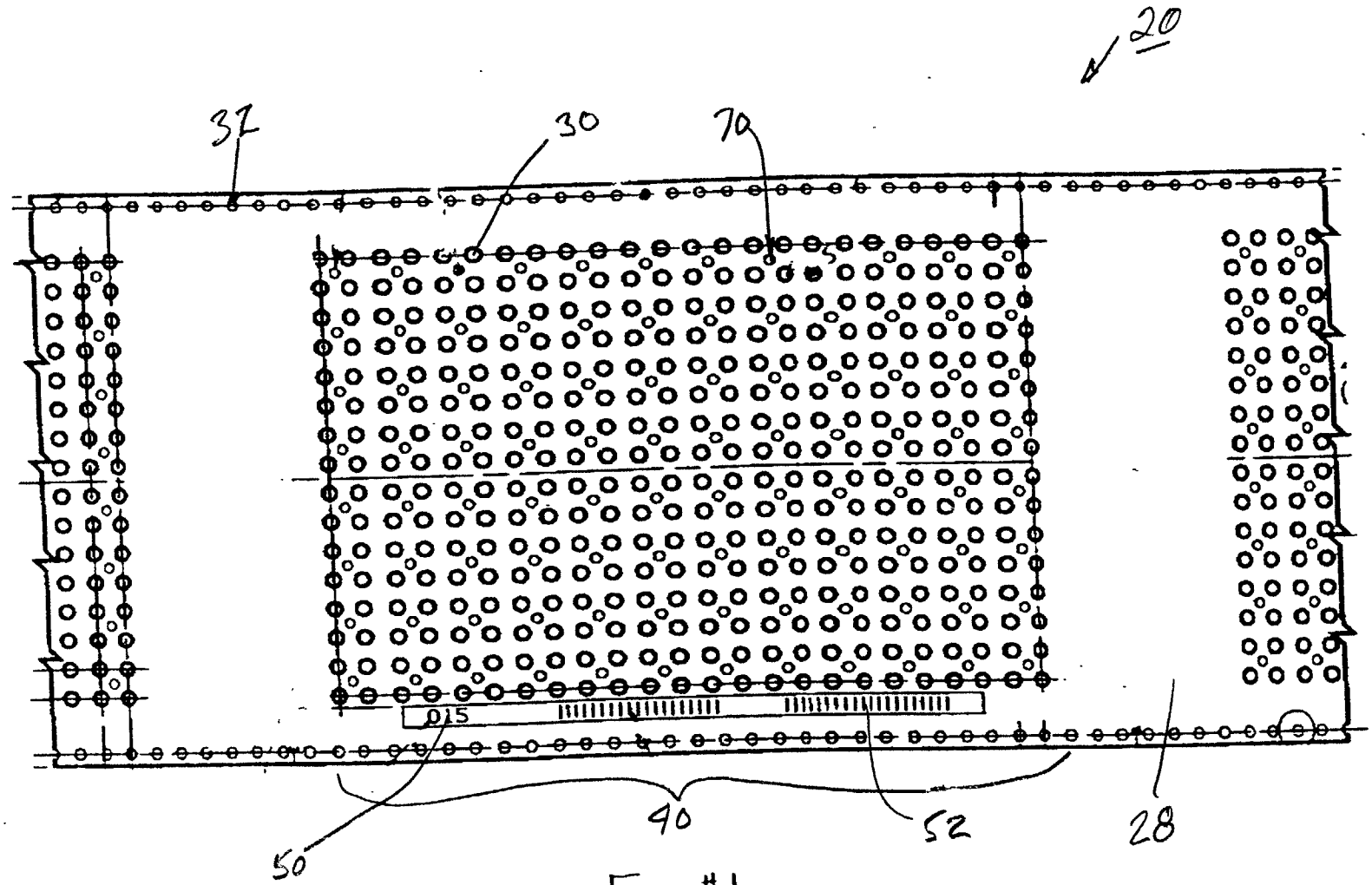

FIG #1

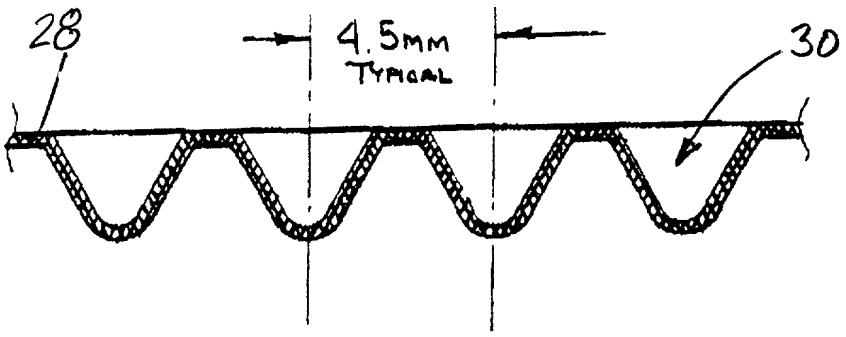

FIG 2

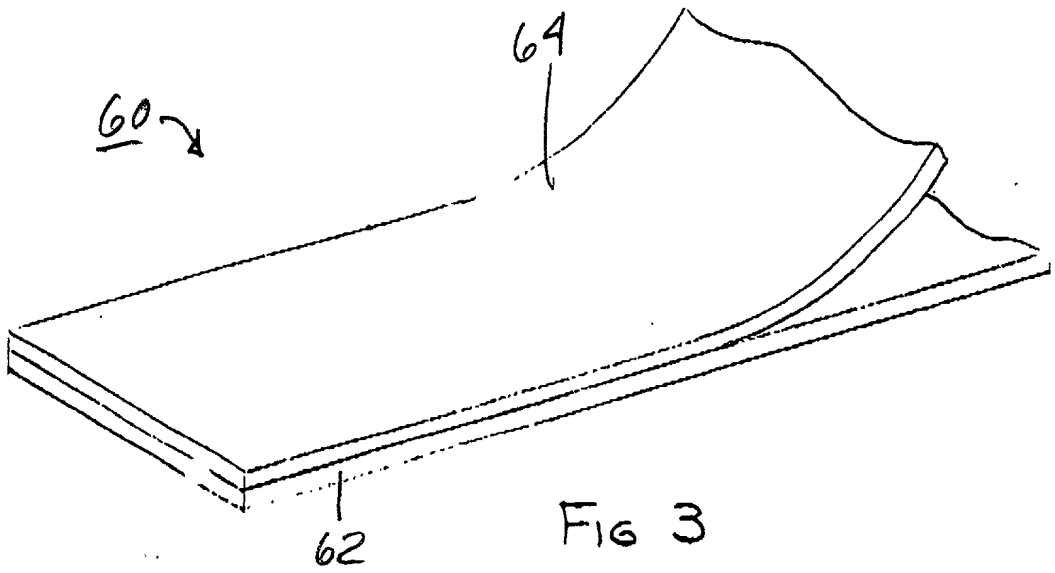

FIG 3

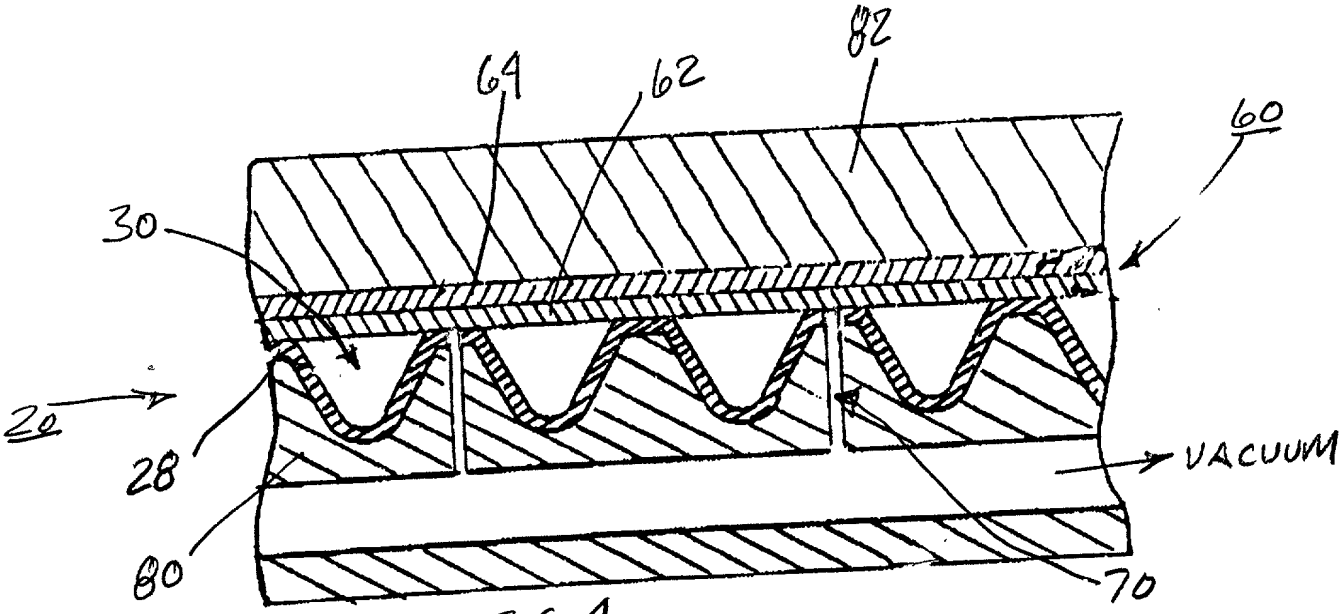

FIG. 4

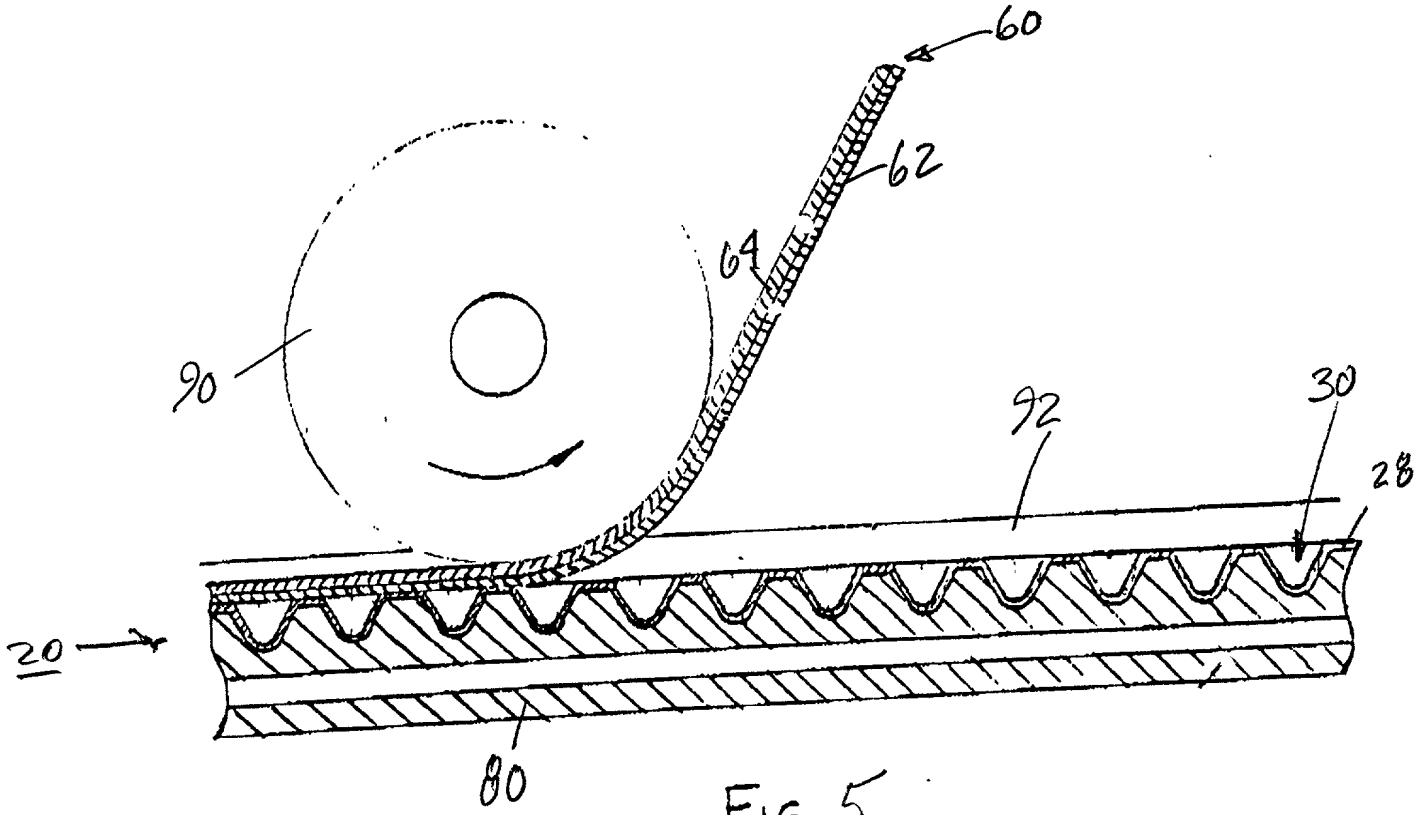

FIG 5

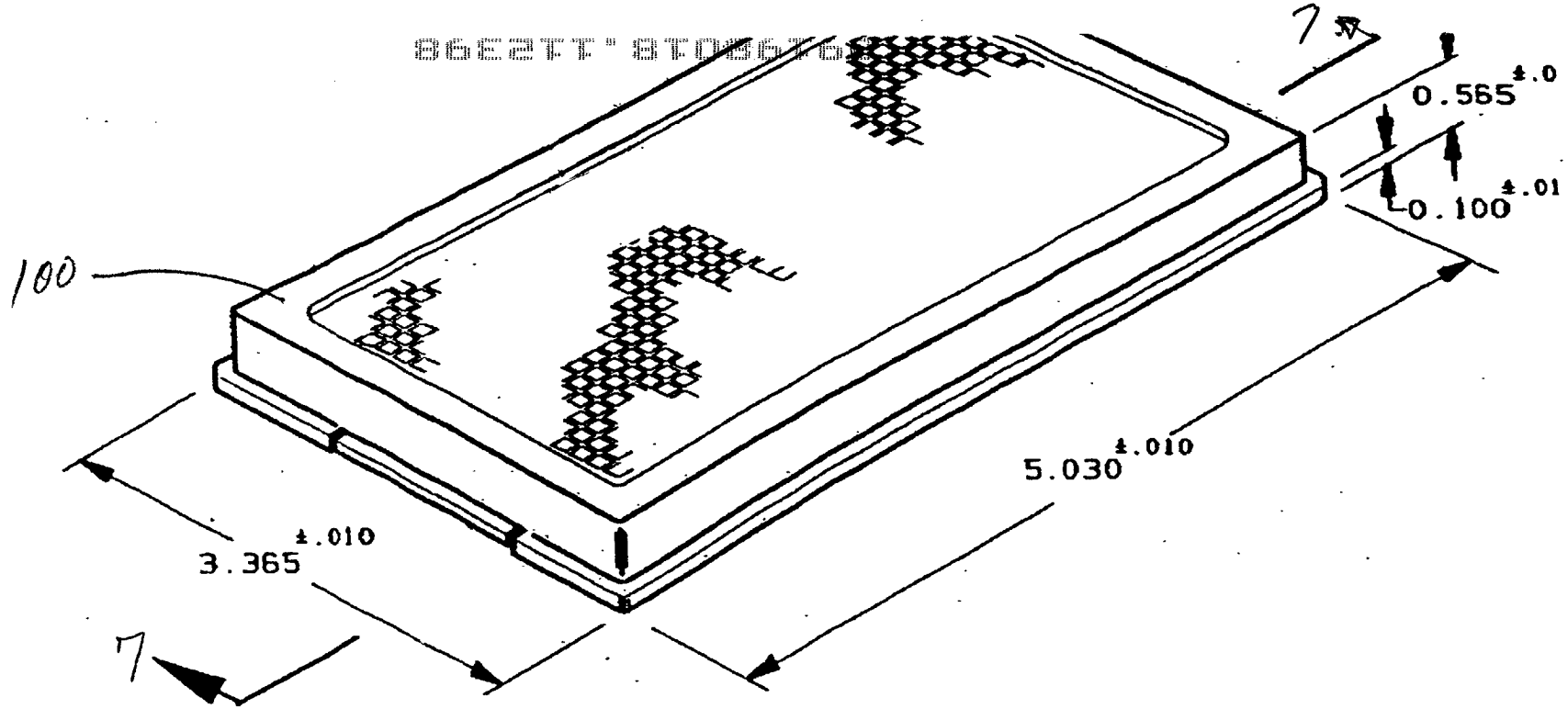

FIG 6

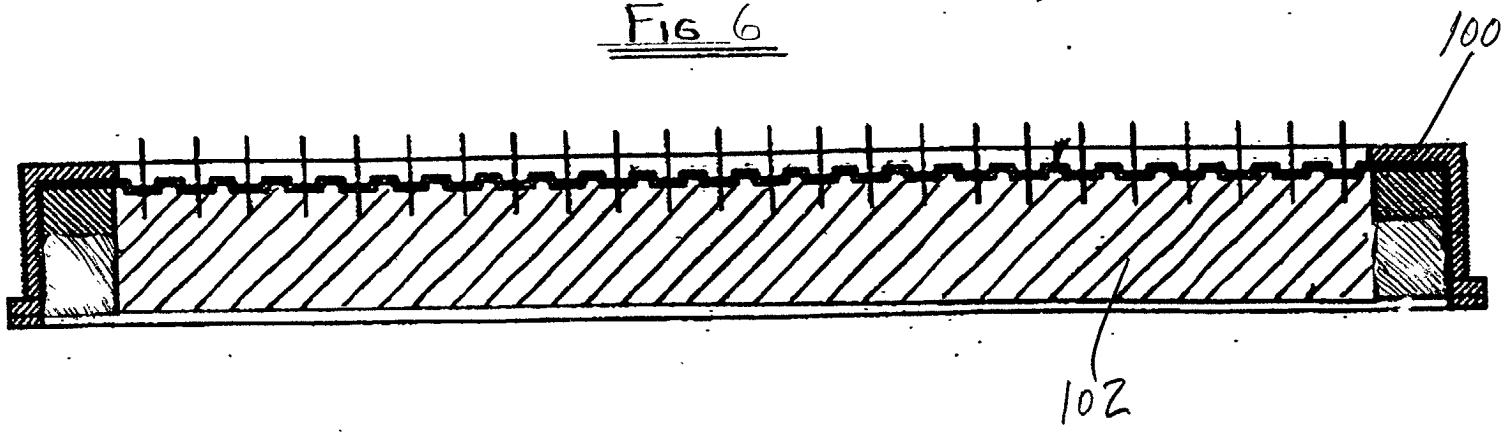

FIG. 7

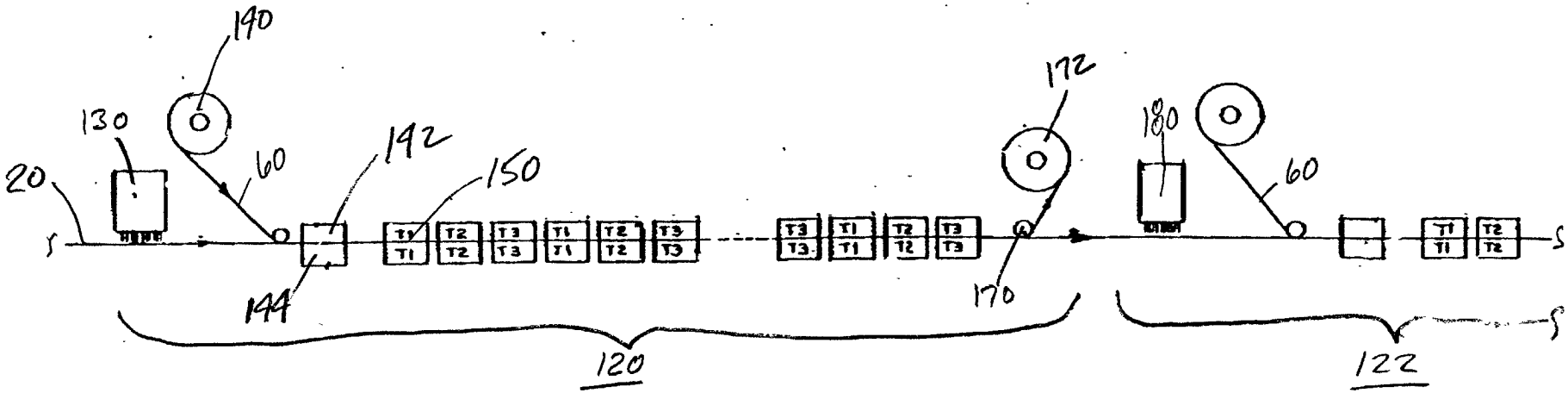

Fig 8

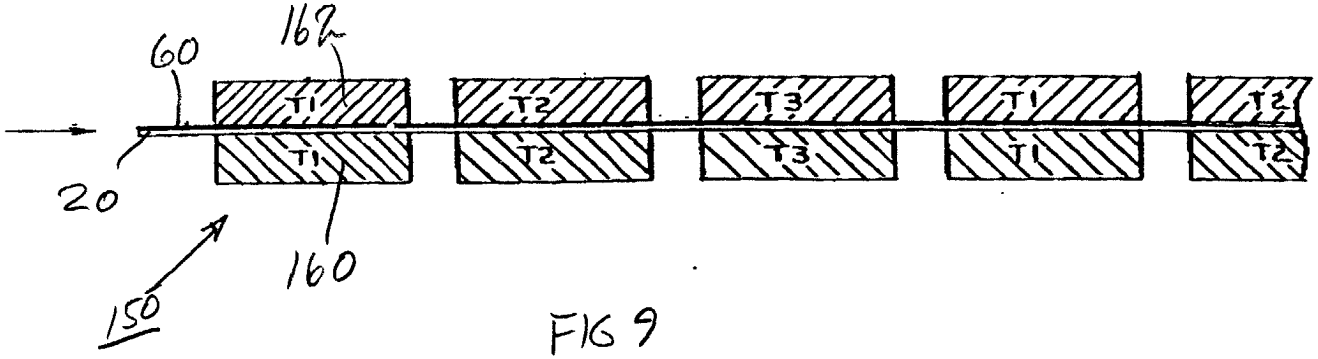

FIG 9

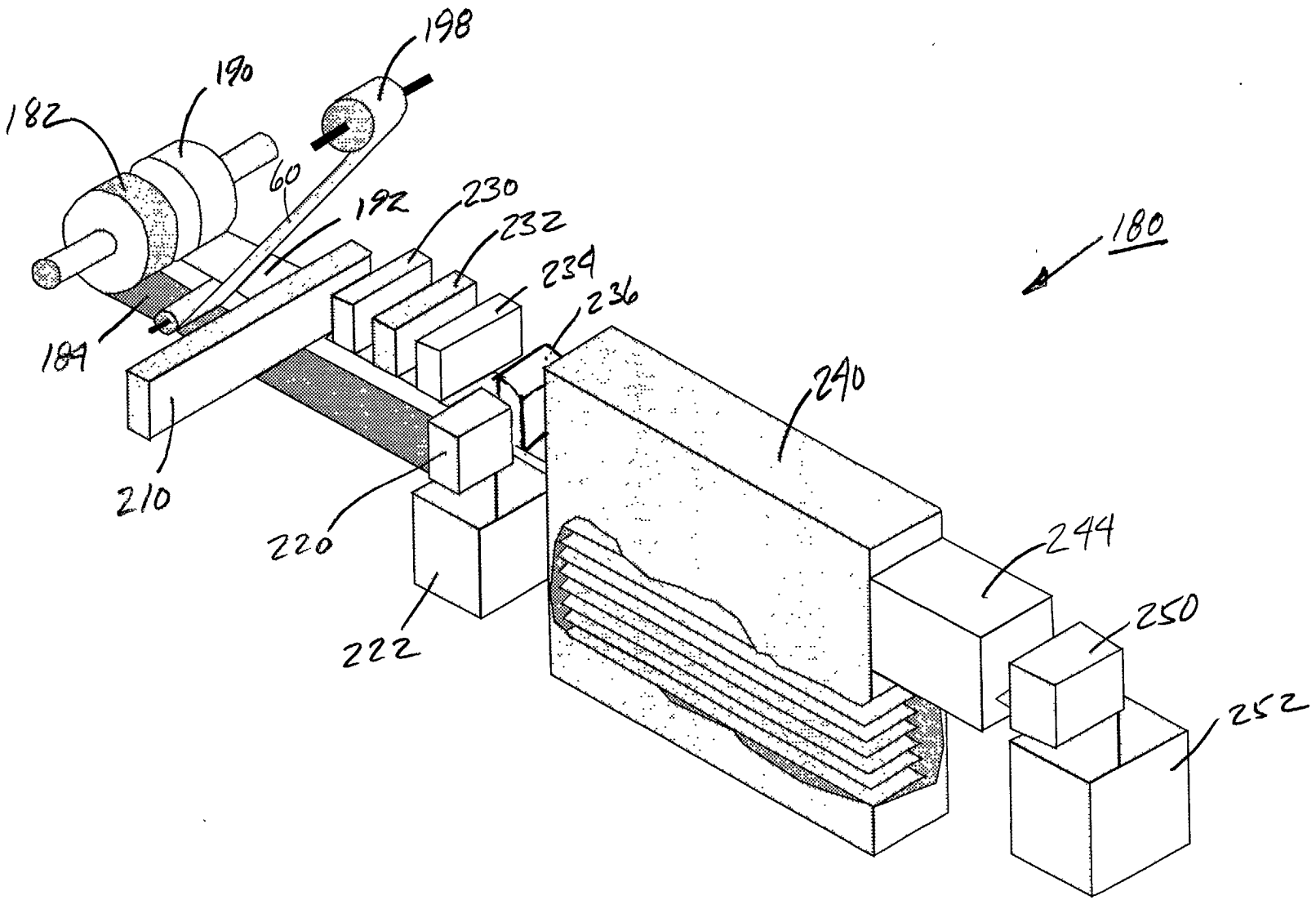
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FIG. 10

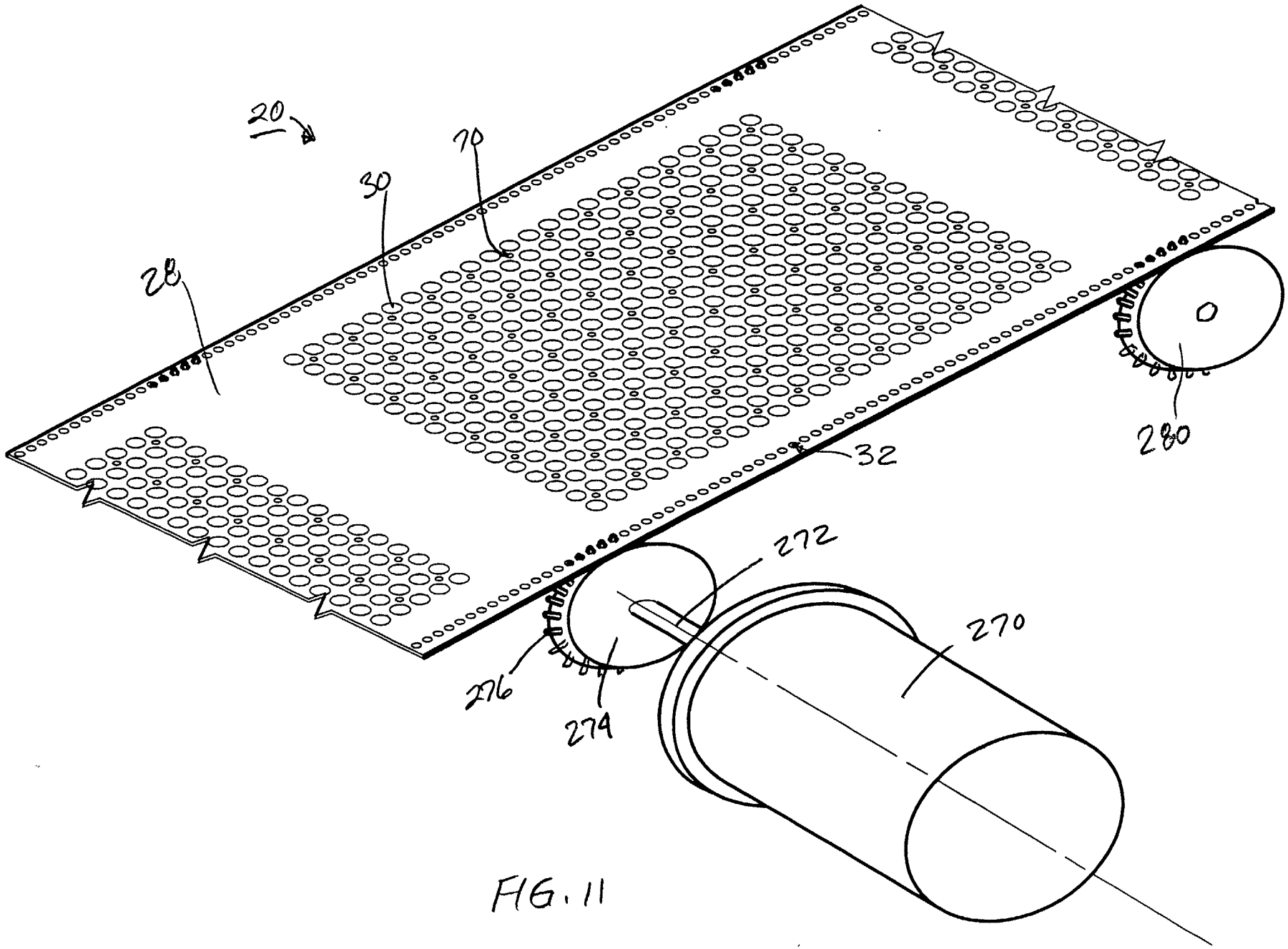

FIG. 11

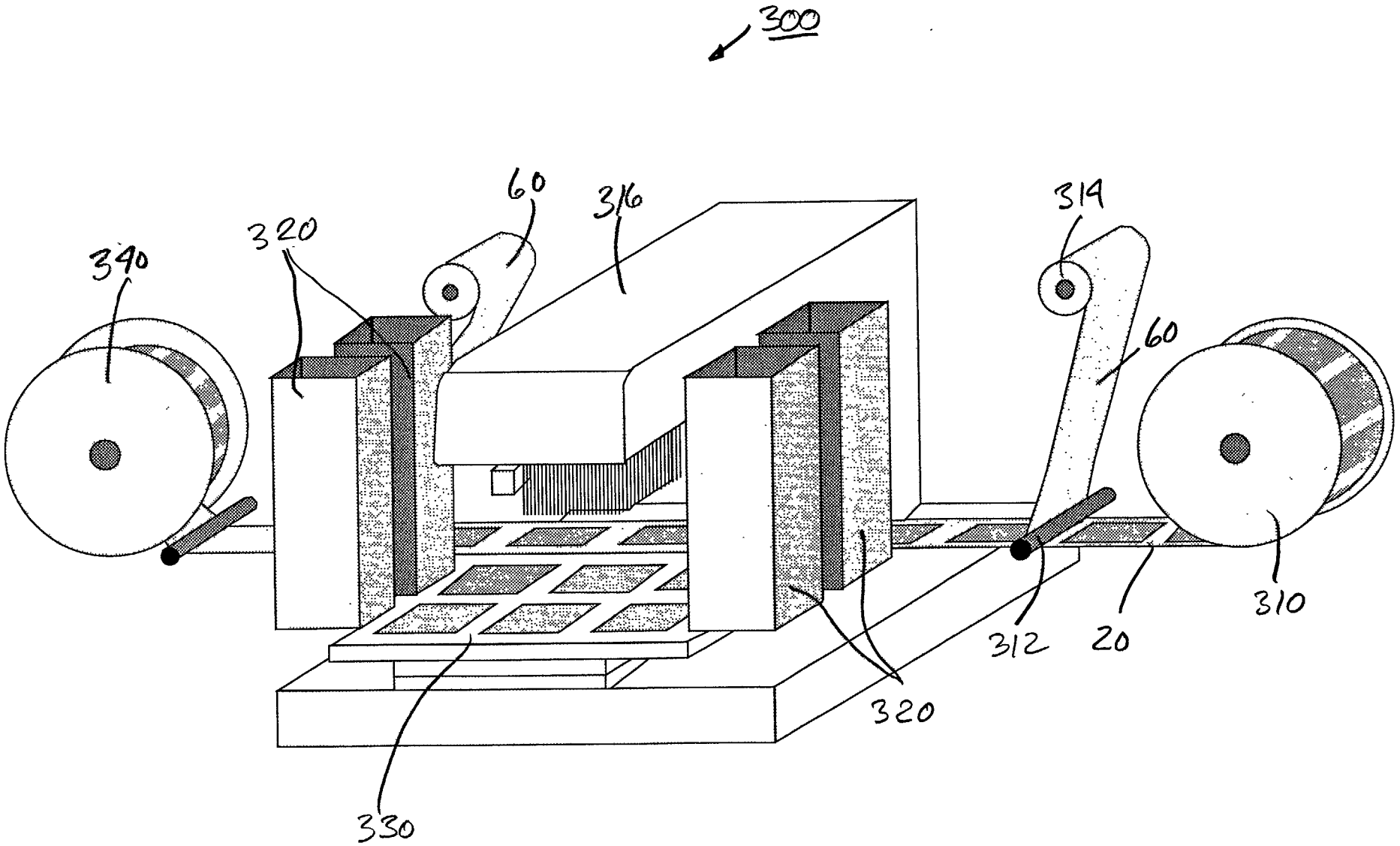

FIG. 12

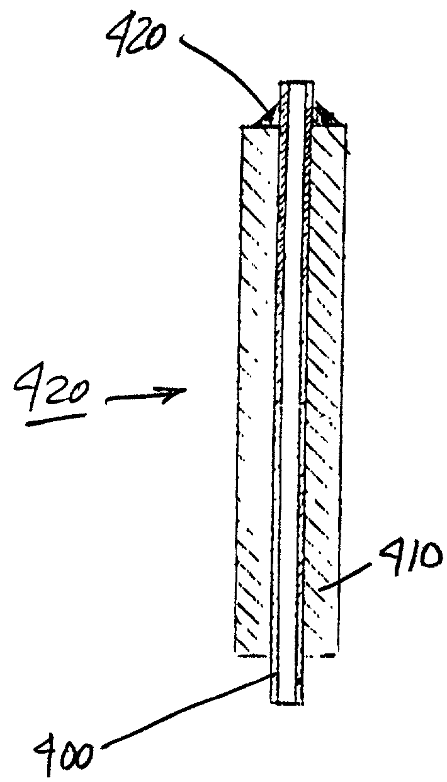

FIG 13

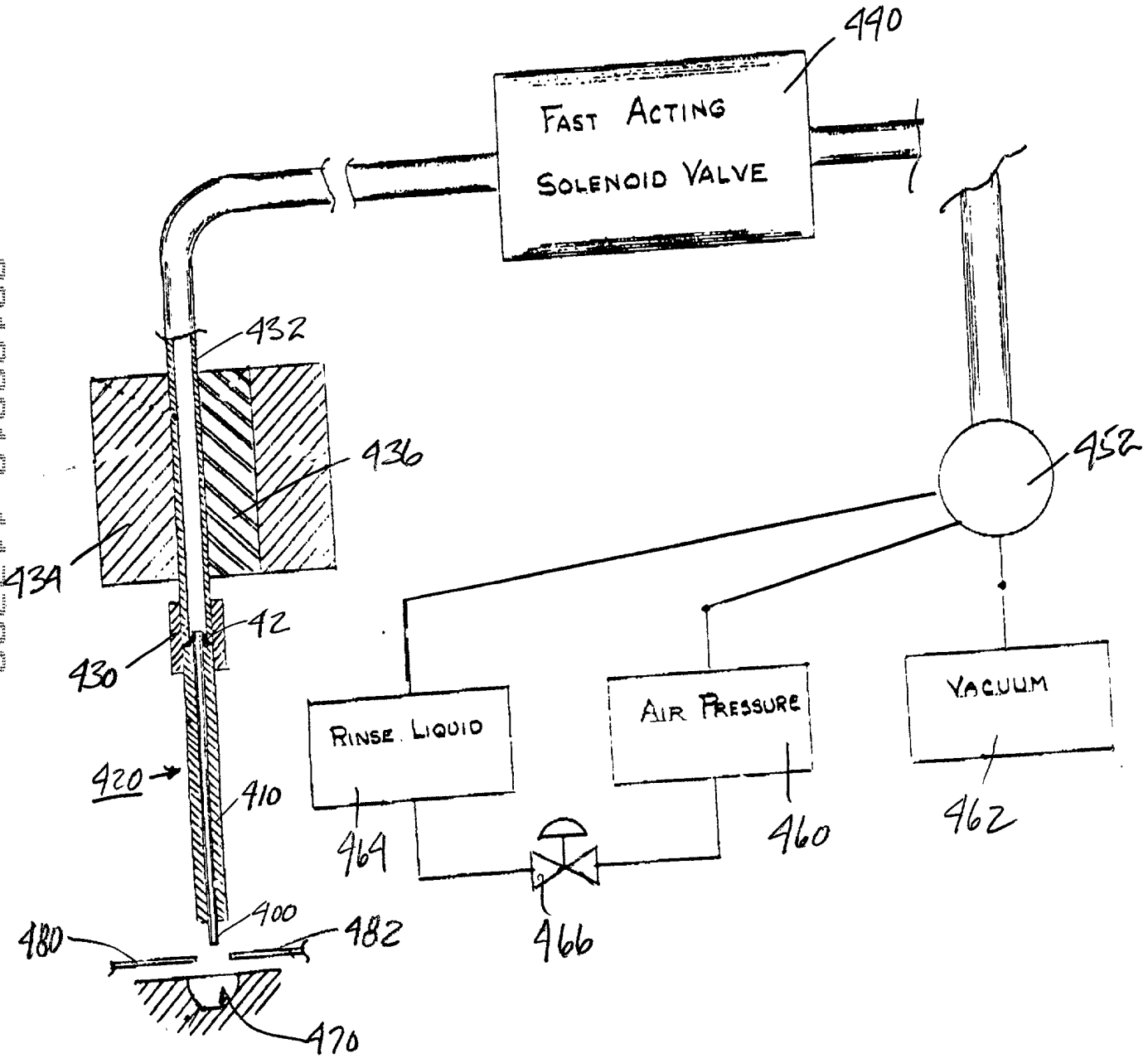
490
FAST ACTING
SOLENOID VALVE
432
436
434
42
430
452
RINSE LIQUID
AIR PRESSURE
VACUUM
420
410
464
460
462
466
400
480
482
470

FIG. 14

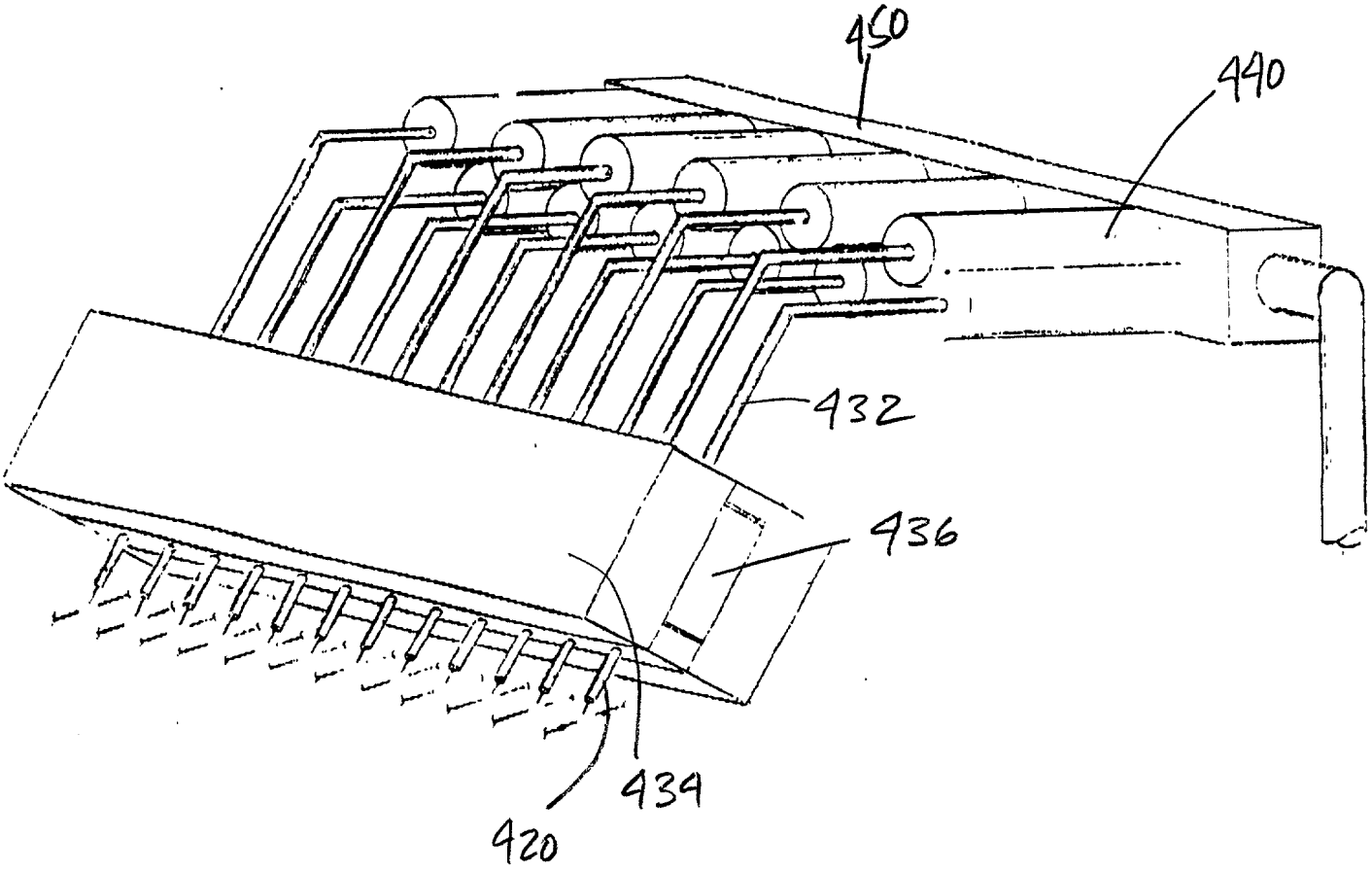

FIG. 15

FTO/SB/01 (4-98)
Approved for use through 9/30/98 OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Type a plus sign (+) inside this box → [+]

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

[X] Declaration Submitted with Initial Filing OR [ ] Declaration Submitted after Initial Filing

Attorney Docket Number	130-125
First Named Inventor	Thomas W. Astle
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ULTRA-HIGH THROUGHPUT BIOASSAY SCREENING SYSTEM

(Title of the invention)

the specification of which

[X] is attached hereto

OR

[ ] was filed on (MM/DD/YYYY) [ ] as United States Application Number or PCT International Application Number [ ] and was amended on (MM/DD/YYYY) [ ] (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)
60/067,895	12/08/97
06/073,329	02/02/98
06/095,497	08/06/98

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

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DECLARATION

Page 2

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
John H. Crozier	30,371		

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

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Address					
City	Trumbull	State	CT	ZIP	06611-5116
Country	US	Telephone	(203) 375-9118	Fax	(203) 378-8108

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name	Thomas	Middle Initial	W.	Family Name	Astle	Suffix e.g. Jr.	

Inventor's Signature: Thomas W Astle Date: Nov 21 1998

Residence: City	Orange	State	CT	Country	06477	Citizenship	US

Post Office Address	
Post Office Address	607 Harborview Road

City	Orange	State	CT	Zip	06477	Country	US

☐ Additional inventors are being named on supplemental sheet(s) attached hereto

Applicant or Patentee: Thomas W. Astle
Serial or Patent No.: _____
Filed or Issued: _____
Title: ULTRA HIGH THROUGHPUT BIOASSAY SCREENING SYSTEM

Attorney's Docket No.: 130-125

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(f) & 1.27(c))--SMALL BUSINESS CONCERN

I hereby declare that I am

☒ the owner of the small business concern identified below:
☐ an official of the small business concern empowered to act on behalf of the concern identified below:
NAME OF SMALL BUSINESS CONCERN Tomtec Inc.
ADDRESS OF SMALL BUSINESS CONCERN 607 Harborview Road
Orange CT 06477

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 13 CFR 121.12, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled ULTRA HIGH THROUGHPUT BIOASSAY SCREENING SYSTEM by inventor(s) Thomas W. Astle
described in

☒ the specification filed herewith
☐ application serial no. _____, filed _____.
☐ patent no. _____, issued _____.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights in the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

NAME _____
ADDRESS _____
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

NAME _____
ADDRESS _____
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Thomas W. Astle
TITLE OF PERSON IF OTHER THAN OWNER President
ADDRESS OF PERSON SIGNING 607 Harborview Road
Orange CT 06477

SIGNATURE Thomas W Astle DATE Nov 21 1998